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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,420	08/10/2001	Sven Mardh	2344-1-001CON	7464

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/18/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/927,420	Sven Mardh
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 5, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above, claim(s) *14-16* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-13, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the search for the preparation of the medicament of group II involves a search of literature relevant to the bacteriophage of group I and for economy of examination groups I and II should be examined together. This is not found persuasive because of the reasons set forth in the Official action mailed 1-29-03 (Paper No. 5). A method of using a bacteriophage for treatment of a bacterial infection differs from a method of using a bacteriophage for manufacture of a medicament. They differ at least in objectives, method steps, reagents and doses used, schedules used, response variables, and criteria of success. They have different classifications and require separate search. Thus, they are patentably distinct from each other.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

Applicant's preliminary amendment filed 10-19-01 has been entered. Claims 4-8, 10 and 12-14 have been amended. Claims 1-16 are pending and claims 1-13 are under consideration.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "**said**," **should be avoided**. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract should be **on a separate page** but **not** the front page of a PCT publication.

4. Claim page, i.e. page 29 of the specification, is objected to because of the following informalities: "I claim", "We claim", or "What is claimed is" should be used on the first line of page 29 but **not** the term "Claim". Appropriate correction is required.

Priority

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Sweden on 2-6-96. It is noted, however, that applicant has not filed a certified copy of the Sweden 9600434-6 application as required by 35 U.S.C. 119(b).

6. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant

application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c).A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Claim Objections

7. Claims 2 and 3 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 2 and 3 are product claims directed to the bacteriophage of claim 1 but fail to further limit the subject matter of claim 1. The use of the bacteriophage in claims 2 and 3 does not further limit the subject matter of claim 1.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,497,874 B1 ('874). Although the conflicting claims are not identical, they are not patentably distinct from each other because, although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 1-12 of the present application are directed to a modified bacteriophage such as M13 bacteriophage, for the treatment or prophylaxis of a bacterial infection *in vitro* and *in vivo*, and the bacteriophage presents at its surface a recombinant protein containing a bacteriophage surface protein, such as gene 3 protein, and a variable region of an antibody, such as ScFv polypeptide, to provide a bacterial antigen binding site.

Claim 1 of '874 is an M13 bacteriophage B8 having the accession No. NCIMB 40779, which is a bacteriophage B8 expressing ScFv-M13 gene 3 fusion protein wherein ScFv is single-chain Fv containing V_H and V_L chains of antibody.

The modified bacteriophage of the present application encompasses the M13 modified bacteriophage B8 of '874, and the claimed invention of the present application would have been obvious for one of ordinary skill at the time of the invention according to the disclosure of '874.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "modified bacteriophage" in claim 1 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "modified bacteriophage". It is unclear what kind of modification of bacteriophage is considered "modified". The specification fails to specifically define the phrase "modified bacteriophage". Claims 2-13 depend on claim 1 but fail to clarify the indefiniteness. Similarly, the phrase "modified filamentous bacteriophage" in claim 4 is vague and renders the claim indefinite. The phrase "modified M13 bacteriophage" in claims 5 and 8 is vague and renders the claims indefinite.

12. Claim 11 recites the limitation "the modified M13 bacteriophage in claim 10" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 10 or 1 does not recite any modified M13 bacteriophage..

13. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: for example, how the bacteriophage is administered to the

mammal, and whether the administration of said bacteriophage ameliorate the bacterial infection in said mammal.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a bacteriophage B8 expressing ScFv-M13 gene 3 fusion protein, wherein ScFv is single-chain Fv containing V_H and V_L chains of antibody against H. pylori antigen and gene 3 is a surface protein of M13 bacteriophage, and shows reduction of H. pylori cell number when infected with said bacteriophage B8 *in vitro*, does not reasonably provide enablement for any modified bacteriophage for use in the treatment or prophylaxis of any type of bacterial infection *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-13 are directed to a modified bacteriophage such as M13 bacteriophage, for the treatment or prophylaxis of a bacterial infection *in vitro* and *in vivo*, and the bacteriophage presents at its surface a recombinant protein containing a bacteriophage surface protein, such as gene 3 protein, and a variable region of an antibody, such as ScFv polypeptide, to provide a

bacterial antigen binding site, a pharmaceutical composition containing said bacteriophage and a pharmaceutically acceptable carrier or excipient, and a method for treatment of a bacterial infection in a mammal by administering said bacteriophage to said mammal.

The specification of the present application disclosed the production of a bacteriophage B8 expressing ScFv-M13 gene 3 fusion protein, wherein ScFv is single-chain Fv containing V_H and V_L chains of antibody against H. pylori antigen and gene 3 is a surface protein of M13 bacteriophage, and shows reduction of H. pylori cell number when infected with said bacteriophage B8 *in vitro*. The claims encompass any modified bacteriophage containing any bacteriophage surface protein and a variable region of an antibody for the treatment of any type of bacterial infection *in vitro* and *in vivo*.

The specification of the present application fails to provide adequate guidance and evidence for how any recombinant phage expressing a phage surface protein and a variable region of an antibody would be able to infect and inhibit the growth of various types of bacterial cells *in vitro* and *in vivo* other than the recombinant phage B8 expressing ScFv-gene 3 fusion protein which reduces the cell number of H. pylori *in vitro*.

A bacteriophage is a virus which specifically infects bacteria, but each bacteriophage has its own range of natural host bacteria. The mechanisms of the survival or invasion of a bacteriophage in its natural host bacteria and non-natural host bacteria could be different and it is unpredictable whether the bacteriophage would survive or have any effect on the non-natural host bacteria. It was well-known in the art that a bacteriophage may not infect all kinds of bacteria

and has its limited host range. Further, the specification of the present application disclosed that the modified bacteriophage B8 decreased CFU of the three H. pylori strains but **did not** affect Staphylococcus or E. coli (bridging page 16, 17). Thus, one skilled in the art at the time of the invention would not know how to use the claimed modified bacteriophage for use in the treatment or prophylaxis of various different bacterial infection.

The specification also fails to provide adequate guidance and evidence for how to administer a modified bacteriophage expressing a recombinant protein containing a bacteriophage surface protein, such as gene 3 protein, and a variable region of an antibody, such as ScFv polypeptide, to a mammal via various administration routes and such administration could provide therapeutic effect for the treatment or prophylaxis of any bacterial infection *in vivo*.

Merril et al., 1997 (US Patent No. 5,688,501) reported that the idea of using phage as a therapy for infectious bacterial diseases was first proposed by d'Herelle in 1918, but this form of therapy was inconsistent and unpredictable in its results because the great potential of these viruses to kill bacteria *in vitro* was not realized *in vivo*. Possible explanation for the viruses being impotent *in vivo* are that the immediate antibody response of the patient against the phage protein upon hypodermic injection, the sensitivity of the phage to inactivation by gastric juices upon oral administration, the facility with which bacteria acquire immunity or sport resistance against phage, and the clearance of viruses by the organs of the reticulo-endothelial systems such as spleen, liver and bone marrow (e.g. column 1-3). Further, administration route of the

modified bacteriophage can affect the amount of the modified bacteriophage to reach target cells so as to provide therapeutic effect *in vivo* and to ameliorate the bacterial infection. In view of such, one skilled in the art at the time of the invention would not know how to use the claimed modified bacteriophage to treat or prevent a bacterial infection *in vivo*.

For the reasons set forth above, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-9 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by McCafferty et al., 1992 (WO 92/01047).

Claims 1-9 and 12 are directed to a modified bacteriophage such as M13 bacteriophage, for the treatment or prophylaxis of a bacterial infection *in vitro* and *in vivo*, and the bacteriophage presents at its surface a recombinant protein containing a bacteriophage surface protein, such as

gene 3 protein, and a variable region of an antibody, such as ScFv polypeptide, to provide a bacterial antigen binding site, and a pharmaceutical composition containing said bacteriophage and a pharmaceutically acceptable carrier or excipient.

McCafferty et al. constructed a phagemid containing gene 3-ScFv fusion gene under the control of lac promoter, wherein ScFv contains V_H and V_L sequence from the antibody D1.3 fused via a peptide linker sequence to form a single chain Fv version of antibody D1.3. The phagemid was used to transform E. coli cells and recombinant phages expressing gene 3-ScFv fusion protein were produced by using M13M07 helper phage (e.g. p. 49, 70, 71, 159). The buffer solution containing the recombinant phages is considered a pharmaceutical acceptable carrier. Thus, claims 1-9 and 12 are anticipated by McCafferty.

18. Claims 1-9 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Winter et al., 1994 (Annual review of Immunology, Vol. 12, pp. 433-455).

Claims 1-9 and 12 are directed to a modified bacteriophage such as M13 bacteriophage, for the treatment or prophylaxis of a bacterial infection *in vitro* and *in vivo*, and the bacteriophage presents at its surface a recombinant protein containing a bacteriophage surface protein, such as gene 3 protein, and a variable region of an antibody, such as ScFv polypeptide, to provide a bacterial antigen binding site, and a pharmaceutical composition containing said bacteriophage and a pharmaceutically acceptable carrier or excipient.

Winter teaches construction of phagemids expressing fusion proteins containing various antibody V fragments and filamentous bacteriophage gene III protein (pIII), and production of recombinant phages particles via rescue with a helper phage M13K07, wherein the fusion proteins containing antibody fragments and pIII are displayed on the surface of the recombinant phages. The phages are selected by binding to antigen, and soluble antibody fragments are secreted from infected E. coli bacteria (e.g., abstract, introduction, p. 435, 436). The buffer solution containing the recombinant phages is considered a pharmaceutical acceptable carrier. Thus, claims 1-9 and 12 are anticipated by Winter.

It should be noted that the intended use of the claimed modified bacteriophage does not carry weight in the 35 U.S.C. 102(b) rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen

Shin-Lin Chen, Ph.D.